Thai Journal of Obstetrics and Gynaecology
January 2009, Vol. 17, pp. 23-29

OBSTETRICS

Preliminary Study : Comparison of the Efficacy of Progesterone and Nifedipine in Inhibiting Threatened Preterm Labour in Siriraj Hospital

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ABSTRACT

Objective: To compare the efficacy, success rate, maternal and fetal complications of progesterone and nifedipine administration as a tocolytic agent to women with threatened preterm labour.

Study Design: A randomized controlled trial.

Materials and methods: During 1st January to 31st May, 2008, a total 40 pregnant women with threatened preterm labour between 28-35 weeks were participated in this study. All women were inhibited contractions randomly with proluton depot 250 mg. intramuscularly weekly or nifedipine 20 mg. orally every 30 minutes for 3 times then maintenance with nifedipine SR 20 mg. every 12 hours until 34 weeks. If neonatal intensive care unit was not available, the inhibition of labour had been prolonged until 36 weeks of gestation. If there was any complication or contraindication with neither proluton depot nor nifedipine, the inhibition method of contractions was changed to be either bricanyl or magnesium sulfate intravenous form.

Results: Forty pregnant women with threatened preterm labour were participated. Eighteen pregnant women were inhibited contractions with proluton depot whilst 22 pregnant women had uterine contraction inhibition with nifedipine. Both groups were not statistically significant in dermographic data, efficacy, mode of delivery and newborn data.

Conclusion: Proluton depot and nifedipine can be used successfully to inhibit contractions in threatened preterm labour. No complication was detected in both groups. Proluton depot seemed to have more efficacy than nifedipine. However, future larger study is needed to confirm the efficacy of both drugs to prevent the process of threatened preterm labour to be preterm labour. This can minimize later preterm birth and decrease both perinatal morbidity and mortality.

Keywords: Proluton depot, Nifedipine, tocolytic, threatened preterm labour

Introduction

Preterm labour is still the main etiology which causes high perinatal morbidity and mortality. The prevalence of preterm labour in Siriraj Hospital is about 8.4%.[1] Siriraj Hospital is the tertiary center where complicated preterm pregnant women have been referred. The limitation of neonatologists and newborn intensive care unit (NICU) resulted in insufficiency care of preterm birth. Therefore, many trials were initiated to inhibit or prevent preterm birth.

The recent evidence from the statistical unit, Siriraj hospital found that threatened preterm labour which had no treatment, turned to be preterm labour about 25%.[1] Some cases were in advanced stage of labour and underwent delivery. Therefore nifedipine[2] and proluton depot were interestingly studied for inhibiting contractions in case of threatened preterm labour. Even though many evidences were suggested to do nothing with threatened preterm labour. Our study suspected that if threatened preterm labour was able to be stopped, the evidence of preterm birth could be minimized as well as perinatal mortality and morbidity.

Definition

Threatened preterm labour was defined as contractions occurring at the frequency of at least 1 time in 10 minutes with no effacement and dilatation of cervix between 20-37 weeks. The examination was taken at least 30 minutes.[3]

Preterm labour was defined as regular uterine contractions 4 times in 20 minutes or 8 times in 60 minutes with progressive cervical dilatation greater than 1 cm and effacement at least 80%.[4]

Successful to stop uterine contractions was defined as no contractions after inhibition of 12 hours.

Non-successful to stop uterine contraction was defined as present contractions during and after inhibition 12 hours.

Recurrent threatened preterm labour was defined as contraction occur after inhibition 12 hours.

Materials and Methods

This study was preliminary study therefore calculation of sample size was not performed. This study was approved by Siriraj Ethics Committee of the Faculty of Medicine Sirriaj Hospital. (However, the next research which compares with control group (no treatment), is still in the process after this preliminary study and approving by Siriraj Ethics Committee of the Faculty of Medicine Sirriaj Hospital.) Forty pregnant women with threatened preterm labour between 1st January to 31st May, 2008, were participated in this study. All were diagnosed as threatened preterm labour which was defined as contractions occurring at the frequency of at least 1 time in 10 minutes with no effacement and dilatation of cervix between 28-35 weeks. If the causes of threatened preterm labour were found, they were treated according to their causes. If the cause could not be defined, inhibition of contractions randomly with 17-alpha-hydroxyprogesterone caproate (proluton depot) or nifedipine continued. Pregnant patients with even number were inhibited with proluton depot and those with odd number with nifedipine. Proluton depot (250 mg.) was given intramuscularly weekly[5] and nifedipine 20 mg was given orally every 30 minutes for 3 times then maintenance with nifedipine SR 20 mg every 12 hours to pregnant women with threatened preterm labour from the diagnosis until 34 weeks of gestation.[2,3] If neonatal intensive care unit was not available, the inhibition of labour would be prolonged until 36 weeks of gestation. If there were any complications with proluton depot, nifedipine or inhibition failure, the inhibition of contractions was changed to be bricanyl intravenous form. If there was contraindication to use bricanyl, magnesium sulfate was used. Maternal vital signs and fetal heart rate monitoring were recorded during the inhibition. After detecting the complications, the inhibition with proluton depot or nifedipine were stopped and replaced with bricanyl intravenously. However, bricanyl was the first line drug which was normally used to inhibit preterm labour at Siriraj Hospital.

Statistical analysis

SPSS version 13 was used to analyze data. Fisher's exact test was used to compare the continuous data. Results were reported as means, standard deviations (SD) or percentages. The level of statistical significance was < 0.05.

Results

During the period of 1st January to 31st May, 2008, a total of 40 pregnant women were admitted at labour room, Siriraj Hospital with the diagnosis of threatened preterm labour. Eighteen and twenty two pregnant women were inhibited contractions with proluton depot and nifedipine, respectively. In the arm of proluton depot, the patient age ranged from 18 to 45 years old with the mean age of 28.3 years old. The gestational age ranged from 28 to 35 weeks with the mean of 31.5 weeks of gestation. The numbers of first, second, third, fourth, sixth and seventh gravida were 8, 3, 4, 1, 1 and 1 cases, respectively.(Table 1) In the arm of nifedipine group, the patient age ranged from 17 to 36 years old with the mean age of 25.8 years old. The gestational age ranged from 29 to 35 weeks with the mean of 31.2 weeks of gestation in the arm of proluton depot group. The numbers of first, second and third gravida were 9, 8 and 5 cases, respectively.(Table 1) By demographic data, both groups were not statistical significant.

In the arm of proluton depot, the contractions of 14 from 18 pregnant women were successful to be inhibited. The contractions of 2, 2, 4, 1, 2 and 3 cases were successful to be inhibited at 1, 2, 3, 4, 5 and 12 hours, respectively. While in the arm of nifedipine, the contractions of 16 from 22 pregnant women were successful to be inhibited. The contractions of 3, 5, 4 and 4 cases were successful to be inhibited at 1, 2, 3 and 4 hours, respectively. Most of the contractions of pregnant women with threatened preterm labour were successful to be inhibited within 5 hours.(Table 2)

In the arm of nifedipine, the contractions of 4 from 18 pregnant women were not successful to be inhibited. The contractions of 1, 2 and 1 cases were failed to be inhibited at 2, 5 and 12 hours, respectively. While in the arm of nifedipine, the contractions of 5 from 22 pregnant women, each were failed to be inhibited at 2, 5, 6, 10 and 12 hours. Recurrent threatened preterm labour was found in one case at 20 hours.(Table 3)

Both groups with proluton depot and nifedipine were not different in mode of delivery, mean gestational age at delivery, mean fetal body weight and mean APGAR score. (Table 4)

Table 1. Demographic data of pregnant patient in both groups who received proluton depot and nifedipine

Data	Proluton depot	Nifedipine
Number of patients	18	22
Maternal age (mean ± SD)	28.3 ± 7.5 (18-45)	25.9 ± 5.7 (17-36)
Gestational age at first administration (mean ± SD)	31.4 ± 1.9 (28-35)	31.2 ± 1.7 (29-35)
Gravida		
1	8	9
2	3	8
3	4	5
4	1	0
6	1	0
7	1	0

Table 2. Number of patients and time of successful contraction inhibition of pregnant patients in proluton depot group and nifedipine group.

Time of inhibition	Proluton depot (n=18)	Nifedipine (n=22)	(Fisher's exact) P-value
Successful after inhibition	(14)	(16)	
1 hour	2 (11.1)	3 (13.6)	1.000
2 hours	4 (22.2)	8 (36.4)	0.491
3 hours	8 (44.4)	12 (54.5)	0.751
4 hours	9 (50.0)	16 (72.7)	0.194
5 hours	11 (61.1)	16 (72.7)	0.509
12 hours	14 (77.8)	16 (72.7)	0.100

Table 3. Number of patients and time of non-successful contraction inhibition of pregnant patients in both groups of proluton depot and nifedipine

Time of inhibition	Proluton depot (n = 4)	Nifedipine (n = 6)
Non-successful after inhibition		
2 hour	1	1
5 hour	2	1
6 hour	0	1
10 hour	0	1
12 hour	1	1
Recurrent preterm labour at 20 hours	0	1

Tabe 4. Delivery and newborn data between the patients in both groups of proluton depot and nifedipine

Data	Proluton depot (n = 18)	Nifedipine (n = 22)
Mode of delivery		
■ Normal delivery	15	19
■ Vacuum extraction (due to non-reassuring fetal status)	0	1
■ Cesarean section (due to non-reassuring fetal status)	3	2
Mean gestational age at delivery (weeks)	36.6 ± 2.6 (35-38)	36.5 ± 1.7 (33-39)
Mean fetal body weight (grams)	2,679 ± 455 (2,350-3,000)	2,547 ± 253 (2,130-3,180)
Mean APGAR score		
■ 1 minute	9	8.8
■ 5 minute	10	10

Discussion

A lot of methods of intervention have been used to prevent preterm labour for a long time.[6] Some interventions including good antenatal care, bed rest, intravenous hydration seemed to improve outcome but there was no strong evidence supporting those intervention in preterm labour prevention.[6] Only fetal fibronectin in cervical mucous and cervical length are used with good evidence based to predict preterm birth.[7,8] However, threatened preterm labour which is classified as regular uterine contractions, can progress to be preterm birth about 25%.[2] Therefore, if this process can be stopped, the chance to become preterm birth could be reduced.

Terbutaline (bricanyl) has been the first line drug which used intravenously or subcutaneously to inhibit preterm labour for over 20 years.[9,10] However, the evidence recently supported that oral form of salbutamol failed to inhibit contraction.[11] Magnesium sulfate has not been approved by FDA for inhibition contraction due to the risk of maternal and fetal morbidity.[12] The study showed that intramuscular progesterone was associated with a reduction in the risk of preterm birth of less than 37 weeks' gestation, and infant birth weight of less than 2500 grams in the patients who had previous history of the preterm birth.[5] Nifedipine was studied and was strongly recommended to inhibit contractions.[5,13] The side effect and complication of nifedipine to mother and fetus are fewer than beta-agonist and magnesium sulfate.[13-15] Therefore, proluton depot and nifedipine were still the promissing medication to use with minimal side effects. There was no study of both drugs in threatened preterm labour. Therefore, proluton depot and nifedipine to inhibit threatened preterm labour are studied.

From the study, proluton depot and nifedipine were successful to inhibit contraction in threatened preterm labour about 77% (14/18 cases) and 73% (16/22 cases), respectively. Mean gestational age at delivery and fetal body weight were also not difference. There was no statistical significance in both groups. Complication of proluton depot and nifedipine in both groups was not detected.

Proluton depot and nifedipine can be similarly used to inhibit contraction in threatened preterm labour. Proluton depot 250 mg can be used intramuscularly weekly while nifedipine 20 mg was given orally every 30 minutes for 3 times then maintenance with nifedipine SR 20 mg every 12

hours. Proluton depot seems to be easy to use but nifedipine has been taken orally many times. Both proluton depot and nifedipine could be used to inhibit threatened preterm labour and needed more studies.

However, this was the preliminary study and sample size was small. Next study needed to be compared with no treatment group which was later approved by Siriraj Ethics Committee of the Faculty of Medicine Sirriaj Hospital. The large study and strong protocol in preterm labour group, not only in threatened preterm labour group, could be proceeded to confirm the efficacy of both drugs.

Acknowledgement

This research never reaches accomplishment without the great help of patients, nurses at labour room and all residents. Our team wants to thank all people mentioned above.

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การศึกษาเบื้องต้นเปรียบเทียบประสิทธิภาพของฮอร์โมน proluton depot และยา nifedipine ในการยับยั้งอาการเจ็บครรภ์คลอดก่อนกำหนดคุกคามในโรงพยาบาลศิริราช

สายฝน ชวาลไพบูลย์, อนุวัฒน์ สุตัณฑวิบูลย์, กาญจนา พิมล, ราตรี ศิริสมบูรณ์, สุพร วรพิทักษานนท์

วัตถุประสงค์ *: เพื่อเปรียบเทียบประสิทธิภาพ, อัตราความสำเร็จ และภาวะแทรกซ้อนของมารดาและทารกในครรภ์จากการใช้ยา proluton depot และ nifedipine ในการยับยั้งอาการเจ็บครรภ์ในกลุ่มสตรีตั้งครรภ์ที่มีภาวะเจ็บคลอดก่อนกำหนดคุกคาม*

ชนิดการวิจัย *: การศึกษาแบบสุ่ม*

วัสดุและวิธีการ *: ระหว่างวันที่ 1 มกราคม พ.ศ. 2551 – 31 พฤษภาคม พ.ศ. 2551 สตรีตั้งครรภ์ที่มีอาการเจ็บครรภ์คลอดก่อนกำหนดคุกคามจำนวน 40 ราย ในช่วงอายุครรภ์ระหว่าง 28-35 สัปดาห์ได้เข้าร่วมในงานวิจัยนี้ สตรีกลุ่มดังกล่าวจะได้รับการยับยั้งอาการเจ็บครรภ์คลอดก่อนกำหนดคุกคามแบบสุ่มด้วยฮอร์โมน proluton depot ขนาด 250 มิลลิกรัม ฉีดเข้ากล้ามสัปดาห์ละครั้ง หรือ nifedipine ขนาด 20 มิลลิกรัมทางปาก ทุก 30 นาที จำนวน 3 ครั้ง จากนั้นต่อด้วย nifedipine SR ขนาด 20 มิลลิกรัม ทุก 12 ชั่วโมง จนถึงอายุครรภ์ 34 สัปดาห์ ในกรณีที่หออภิบาลทารกแรกคลอดเต็ม การยับยั้งอาการเจ็บครรภ์คลอดก่อนกำหนดจะดำเนินต่อจนถึงอายุครรภ์ 36 สัปดาห์ ในกรณีที่เกิดภาวะแทรกซ้อนจากฮอร์โมน proluton depot หรือ nifedipine จะเปลี่ยนวิธีการยับยั้งอาการเจ็บครรภ์คลอดก่อนกำหนดไปใช้ยา bricanyl ทางหลอดเลือดหรือยา magnesium sulphate ต่อไปตามลำดับ*

ผลการศึกษา *: สตรีตั้งครรภ์ที่มีภาวะเจ็บครรภ์คลอดก่อนกำหนดคุกคามจำนวน 40 ราย ได้เข้าร่วมในการศึกษา 18 รายถูกยับยั้งอาการเจ็บครรภ์คลอดก่อนกำหนดด้วยฮอร์โมน proluton depot ในขณะที่ 22 รายได้ยา nifedipine ทั้ง 2 กลุ่ม ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในข้อมูลพื้นฐานทั่วไป ประสิทธิภาพของยา การคลอดและข้อมูลพื้นฐานของทารกแรกคลอด*

สรุป *: proluton depot และ nifedipine สามารถนำมาใช้ในการยับยั้งอาการเจ็บครรภ์คลอดก่อนกำหนดคุกคามได้สำเร็จ ไม่พบภาวะแทรกซ้อนของยาทั้ง 2 ตัว สำหรับ proluton depot ดูเหมือนจะมีประสิทธิภาพมากกว่ายา nifedipine อย่างไรก็ตามยังต้องการการศึกษาที่มีขนาดใหญ่ต่อไปในอนาคตเพื่อยืนยันถึงประสิทธิภาพของยาทั้ง 2 ในการป้องกันขบวนการเจ็บครรภ์คลอดก่อนกำหนดคุกคามไม่ให้เป็นภาวะเจ็บครรภ์คลอดก่อนกำหนด เพื่อช่วยลดทารกก่อนกำหนด ความพิการและการตายของทารกแรกคลอด*